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Relation of Coronary Artery Stenosis and Pressure Gradient to Exercise-Induced Ischemia Before and After Coronary Angioplasty

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The purpose of this investigation was to evaluate the relation of coronary artery stenosis and associated pressure gradient to the magnitude of exercise-induced left ventricular dysfunction in patients with single vessel coronary artery disease. The percent stenosis and minimal cross-sectional area were measured before and after percutaneous transluminal coronary angioplasty and compared with radionuclide measurements of left ventricular function before and after angioplasty in 41 patients with proximal left anterior descending coronary artery lesions, providing 82 points of comparison. The gradient could be measured for 75 comparisons.

Forty stenoses <50% were associated with a mean left ventricular exercise ejection fraction of 0.66 ± 0.08 (mean ± SD), 25 stenoses from 50 to 75% with a mean ejection fraction of 0.59 ± 0.12 and 17 stenoses >75% with a mean ejection fraction of 0.49 ± 0.08. Thirty-five stenoses with a gradient <20 mm Hg were associated with a mean ejection fraction of 0.65 ± 0.09, 24 with a gradient from 20 to 50 mm Hg with a mean ejection fraction of 0.58 ± 0.13 and 16 with a gradient >50 mm Hg with a mean ejection fraction of 0.53 ± 0.10.

These data document a relation between the magnitude of coronary artery stenosis and associated gradient to exercise-induced left ventricular dysfunction in homogeneous patient groups. However, discordance of these variables occurs commonly in individual patients.

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The severity of a coronary artery lesion does not always correlate with the severity of its ischemic complications. The discordance between the physiologic response of patients with similar anatomy remains poorly understood. Percutaneous transluminal coronary angioplasty provides measurements of constriction and pressure gradient across stenotic lesions in patients (1). During exercise, patients with coronary artery disease frequently demonstrate abnormalities in left ventricular function before angina pectoris or electrocardiographic (ECG) evidence of myocardial ischemia develops (2,3). The purpose of this investigation was to evaluate relations of coronary artery stenosis and associated gradient to the magnitude of exercise-induced left ventricular dysfunction in patients with single vessel coronary artery disease.

Methods

Study patients. From October 1, 1981 to October 1, 1982, 294 patients undergoing percutaneous transluminal coronary angioplasty at Emory University Hospital had a left anterior descending coronary artery lesion. Patients with an isolated proximal left anterior descending lesion and no stenosis >50% of any other coronary artery were considered candidates for this study. Patients with a history of coronary artery bypass grafting, cardiac valvular replacement, congestive heart failure, radiographic or ECG evidence of left ventricular hypertrophy or a hemodynamically significant myocardial infarct, defined here as a left ventricular ejection fraction of less than 0.45 at a rest radionuclide angiographic study before angioplasty, were excluded. Additional criteria for myocardial infarction were reviewed, including each patient's clinical records, data bank information and ECG data. No patient had a previous anterior myocardial infarct. ECG data from two patients did reveal changes consistent with previous inferior myocardial in-

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Table 1. Effect of Coronary Stenosis Severity on Exercise Ejection Fraction (82 measurements in 41 patients)

Stenosis Severity (%)	No. of Comparisons	Percent Abnormal Exercise Ejection Fraction (<0.59) (%)	Mean Exercise Ejection Fraction
<50	40	23	0.66 ± 0.08
			$p < 0.01$
50 to 75	25	48	0.59 ± 0.12
			$p < 0.05$
>75	17	94	0.49 ± 0.08

farction; their inclusion or exclusion did not alter statistical findings in any way. Studies were performed only on those patients in whom discontinuation of beta-adrenergic blocking medications for at least 24 hours before radionuclide study was considered safe. Failure to discontinue beta-blocking medication was the most common reason for exclusion from the study. All other medications taken before, during and after angioplasty were recorded.

Selection criteria were met in 41 patients, 35 male and 6 female, with a mean age of 53 ± 9 years (range 35 to 70). In 23 patients the left anterior descending artery lesion was proximal to the first septal perforator, and in 18 patients the lesion was distal but within 1 cm of the first septal perforator.

Measurement of lesion severity. Angioplasty of an isolated proximal left anterior descending coronary artery lesion was performed and patients were managed by a described technique (1). The percent diameter stenosis of coronary artery lesions on cineangiograms was measured using an electronic caliper immediately before and after angioplasty by comparing the diameter of the narrowest point of stenosis with the average diameters just proximal and just distal to the stenosis. Measurements were repeated in every view in which the lesion was seen, and the mean percent diameter stenosis was expressed as the average of those several measurements. The minimal diameter was determined for each stenosis before and after angioplasty utilizing the catheter as the reference point. Minimal diameter was averaged from two views and expressed in millimeters. The minimal cross-sectional area was then determined by the formula $\pi \times \text{minimal diameter}^2/4$.

Simultaneous equisensitive pressure measurements were obtained using Statham P23db strain gauges through fluid-filled catheters 1.1 mm in diameter. Pressures from two ports, one at the tip of the guidance catheter and one near the end of the balloon dilation catheter, were calibrated before crossing the lesion. The gradient was recorded as the difference in the mean pressures on each side of the lesion (1).

Radionuclide angiocardiography. First pass radionuclide angiocardiograms were obtained within 24 hours before and again 2 to 3 days after angioplasty. Data were acquired in the anterior projection using a multicrystal gamma camera (Baird System Seventy-Seven) with a 1 inch (2.54 cm) parallel hole collimator. A 10 mCi bolus of technetium-99m pertechnetate was injected through a 20 gauge Teflon catheter inserted into an antecubital vein, and data were recorded at 25 ms intervals for a 1 minute period. Patients were seated erect for the rest study. Blood pressure and heart rate were recorded at 1 minute intervals and the ECG was continuously monitored. Upright exercise was begun on a Quinton model 845 constant work load bicycle ergometer at an initial work load of 200 kp-m and increased by 100 kp-m every minute until 85% of the age-predicted maximal heart rate was reached (3–6). End points of exercise before injection were defined as muscle fatigue, marked shortness of breath, onset of typical angina associated with a 1 mm depression of the ST segment, a ≥2 mm depression of the ST segment with or without symptoms, a life-threatening arrhythmia, hypotension or attainment of target heart rate. During exercise at the target heart rate or exercise end point, a second 10 mCi bolus of technetium-99m pertech-

Table 2. Effect of Coronary Gradient Severity on Exercise Ejection Fraction (75 measurements)

Gradient Severity (mm Hg)	No. of Comparisons	Percent Abnormal Exercise Ejection Fractions (<0.59) (%)	Mean Exercise Ejection Fraction
<20	35	29	0.65 ± 0.09
			$p < 0.01$
20 to 50	24	54	0.58 ± 0.13
			$p < 0.001$
			$p = NS$
>50	16	75	0.53 ± 0.10

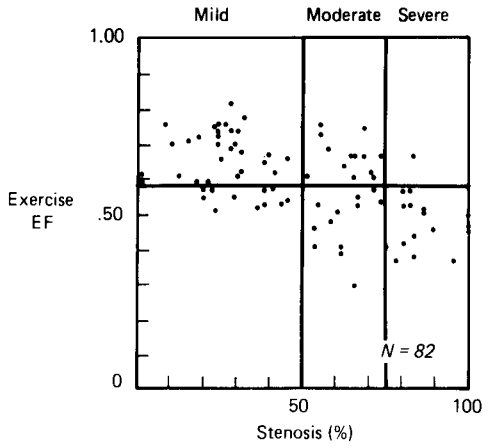


Figure 1. Individual comparisons of stenosis severity and exercise left ventricular ejection fraction (EF). Normal exercise ejection fractions (≥0.59) are above the **horizontal line** and abnormal exercise ejection fractions (<0.59) are below the **horizontal line.** Eighty-two measurements were made before and after coronary angioplasty in 41 patients.

netate was injected with data again collected at 25 ms intervals over a 1 minute period. After exercise, patients were monitored in the supine position until heart rate, blood pressure and all symptoms returned to baseline levels.

One or two days after angioplasty, rest and exercise radionuclide studies were again repeated before discharge from the hospital. The exercise end point for the second study was the heart rate achieved during the initial exercise study.

Data analysis. Radionuclide data for each study were processed by well described methods (7–9). Data analyzed included systemic blood pressure, heart rate, maximal work load, exercise duration, symptoms developed during exercise, rhythm strip ECG changes, left ventricular ejection fraction, end-diastolic and end-systolic volumes, stroke volume and cardiac output. Representative cardiac cycles were generated from multiple left ventricular beats to assess wall motion abnormalities. Studies with abnormal left ventricular wall motion during exercise were reprocessed to determine regional ejection fraction from the anterior and posterior segments of the left ventricle. The exercise ejection fraction, coronary stenosis and gradient were related by regression analysis and by subgrouping magnitude of stenosis and gradient. A stepwise linear regression was performed to evaluate the influence of stenosis severity and gradient severity and site of the left anterior descending lesion (proximal to or within 1 cm distal to the first septal perforator) (10). Individual stenosis and gradient measurements were also regressed as single variables against exercise left ventricular ejection fraction to determine linearity of these relations.

The designation of an exercise ejection fraction of <0.59 as an abnormal functional response in the tables and figures is somewhat arbitrary, though it is based on a value that best separated more than 1,000 patients with angiographic presence or absence of coronary artery disease (11). However, analysis of individual data in this study was primarily based on absolute values of exercise left ventricular ejection fraction.

Results

Relation between severity of stenosis and exercise ejection fraction. Group relations were documented between the severity of stenosis and exercise-induced left ventricular dysfunction in this homogeneous patient population. Mean exercise ejection fraction was significantly different in each of the three categories of stenosis severity (Table 1). All but 1 of the 17 stenosis measurements >75% were associated with an abnormal exercise ejection fraction. Similar comparisons were made between exercise left ventricular dysfunction and various gradients across a lesion. Although group associations existed between categories of severity of gradient and exercise-induced left ventricular dysfunction, differences were less marked than those for the categories of stenosis severity (Table 2).

Individual variations in the relation of lesion severity to ventricular dysfunction are often observed clinically. The 82 comparisons of stenosis measurements to exercise left ventricular ejection fraction were individually plotted (Fig. 1). Although the majority of mild stenoses (<50%) were associated with a normal exercise ejection fraction response and almost every severe stenosis (>75%) was associated with an abnormal response, the lowest exercise ejection fraction was not associated with the most severe stenosis. This emphasizes the individual variation of response, particularly seen in the group with intermediate stenosis. For instance, one stenosis measurement of 65% was associated with an exercise ejection fraction of 0.31, whereas another stenosis measurement of 68% was associated with an ex-

Figure 2. Individual comparisons of minimal cross-sectional area and exercise left ventricular ejection fraction (LVEF) (n = 82).

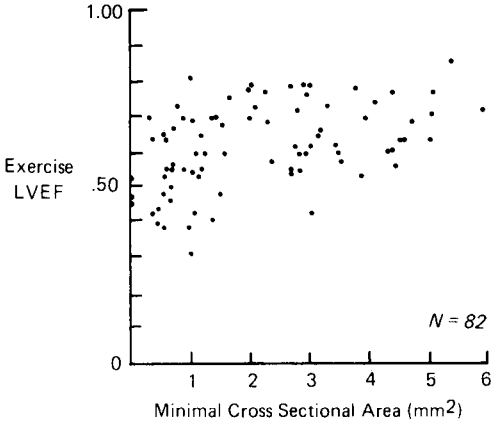


Table 3. Rest to Exercise Change in Left Ventricular Ejection Fraction Relative to Lesion Severity in 41 Patients

	Change in Left Ventricular Ejection Fraction		
	<-5	-5 to $+5$	$>+5$
Stenosis (%)	72 ± 20	44 ± 23	33 ± 20
		$p < 0.00001$	$p < 0.06$ = NS
		$p < 0.00001$	
Minimal cross-sectional area (mm^2)	1.03 ± 1.2	2.28 ± 1.4	3.24 ± 1.4
		$p < 0.0004$	$p < 0.01$
		$p < 0.00001$	

ercise ejection fraction of 0.76. The relation of stenosis severity to exercise ejection fraction was nonlinear ($r = -0.53$). Similar general associations were found when the minimal cross-sectional area was determined in place of percent stenosis (Fig. 2).

Patients whose left ventricular ejection fraction decreased from rest to exercise had a significantly greater mean stenosis (65 ± 22%) than did patients whose ejection fraction was unchanged or increased (38 ± 23%, $p < 0.00001$). The minimal cross-sectional area was also significantly less for studies in which left ventricular ejection fraction decreased from rest to exercise (1.26 ± 1.2 mm^2) than those in which it was unchanged or increased (2.82 ± 1.4 mm^2, $p < 0.00001$). Differences were even more marked when studies were divided into those with a >5% increase or decrease in ejection fraction (Table 3, Fig. 3 and 4).

Relation between gradient severity and exercise ejection fraction. A greater degree of individual variation existed between the 75 measurements of gradient severity and their associated exercise ejection fraction response (Fig. 5). Again, the most pronounced variations in the relations of lesion severity to left ventricular function occurred in the group with intermediate gradient severity. The relation of gradient to exercise ejection fraction was nonlinear ($r = -0.43$). The 75 gradient measurements were compared with stenosis and minimal cross-sectional area measurements of the same lesions (Fig. 6 and 7). Low degrees of stenosis were associated with a low gradient and more severe stenosis with much greater variation in gradient measurements. Marked individual variation between stenosis measurements and the associated gradient existed even in the group of most severe stenosis (>75%). The largest gradient measurements were not associated with the most severe stenosis measurements.

Results before and after coronary angioplasty. Measurements of exercise left ventricular function were obtained both before and after angioplasty to compare function over a broad range of lesion severity. The majority of patients exhibited an improved exercise ejection fraction after angioplasty (Fig. 8). In general, patients with the lowest exercise ventricular ejection fraction before angioplasty demonstrated the greatest improvement in exercise ventricular function after angioplasty.

Multivariate analysis. Forty-six data points represented lesions proximal to the first septal perforator of the left anterior descending coronary artery. The remaining 36 lesions were within 1 cm distal to the first septal perforator by study design. Multivariate regression analysis failed to separate lesion location as a significant variable.

Figure 3. Change in left ventricular ejection fraction (LVEF) from rest to exercise versus stenosis severity (n = 82).

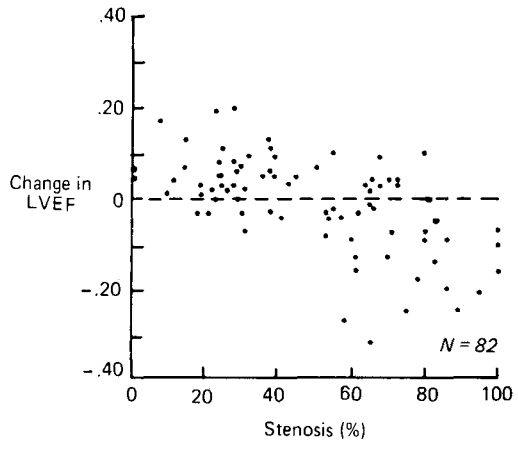
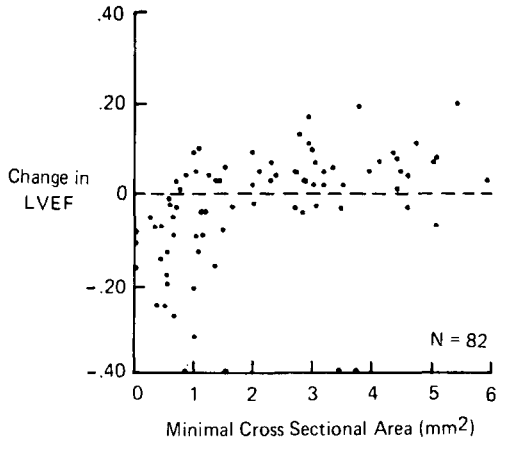


Figure 4. Change in left ventricular ejection fraction (LVEF) from rest to exercise versus minimal cross-sectional area (n = 82).



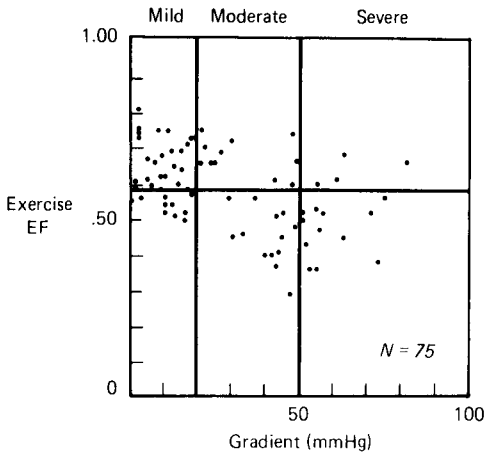


Figure 5. Individual comparisons of pressure gradient severity and exercise left ventricular ejection fraction (EF) (n = 75).

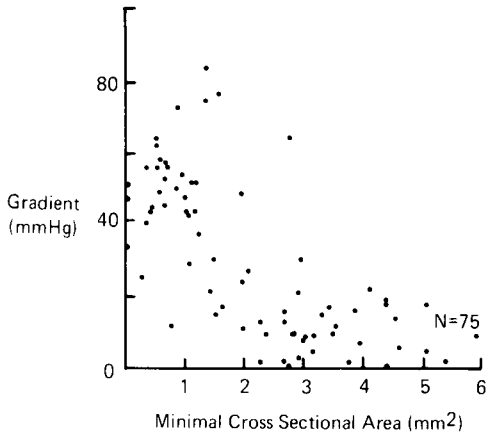


Figure 7. Individual comparisons of gradient severity and minimal stenosis cross-sectional area (n = 75).

The three variables of exercise left ventricular ejection fraction, percent stenosis and gradient were related by multivariate analysis. When exercise ejection fraction was held as the dependent variable, the relation to percent stenosis was significant ($p < 0.0001$). However, the relation to gradient severity was not significant. With percent stenosis held as the dependent variable, both exercise ejection fraction and gradient were significantly related ($p < 0.002$ and $p < 0.0001$, respectively). Simultaneous comparison of the measurements of stenosis and gradient with exercise left ventricular function demonstrated that exercise ejection fraction responses tended to be normal when both stenosis and gradient measurements were mild and tended to be abnormal when both stenosis and gradient measurements were severe. As predicted from the regression analysis when measurements of stenosis and gradient did not agree, severe stenosis correlated with abnormal ejection fraction responses more consistently than did severe gradient (Fig. 9).

Correlation with wall motion abnormalities and end-systolic volume. Chi-square analysis has shown exercise left ventricular ejection fraction to carry greater information in correlation to severity of coronary artery disease than any other variable analyzed (12). However, exercise left ventricular wall motion and end-systolic volume may also be analyzed. Percent diameter stenosis did correlate to wall motion abnormalities. Ninety percent of patient studies with a stenosis <20% and 80% of studies with a stenosis between 20 and 50% had normal left ventricular wall motion during exercise whereas 71% of studies with a stenosis >50% had abnormal wall motion (Table 4). This correlation could also be demonstrated in terms of cross-sectional area. Patients with normal left ventricular wall motion during exercise had a minimal cross-sectional area of 2.98 ± 1.3 mm^2, whereas those with abnormal wall motion had a mean cross-sectional area of only 1.12 ± 1.03 mm^2 ($p < 0.00001$).

Figure 6. Relations of coronary stenosis (percent diameter narrowing) to gradient (mean pressure across the lesion) (n = 75).

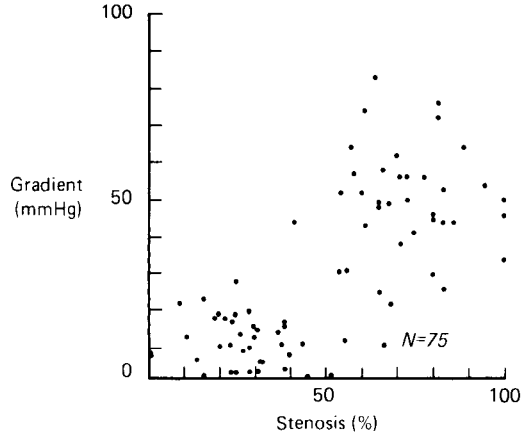
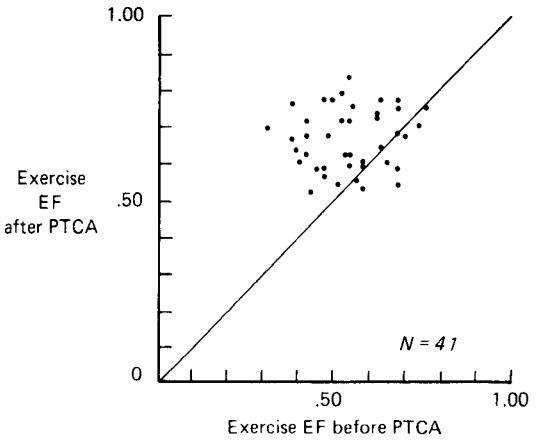


Figure 8. Comparison of exercise left ventricular ejection fraction (EF) measured before and after percutaneous transluminal coronary angioplasty (PTCA) in 41 patients. The **solid line** is the line of identity.



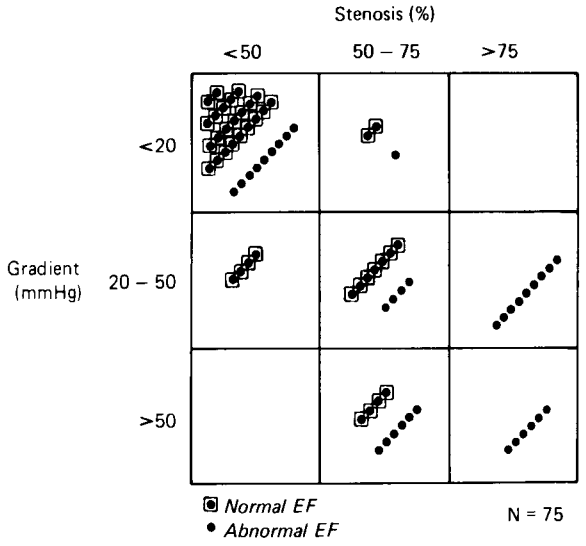


Figure 9. Simultaneous comparison of stenosis and gradient measurements of 75 coronary lesions with associated measurements of exercise left ventricular ejection fraction (EF).

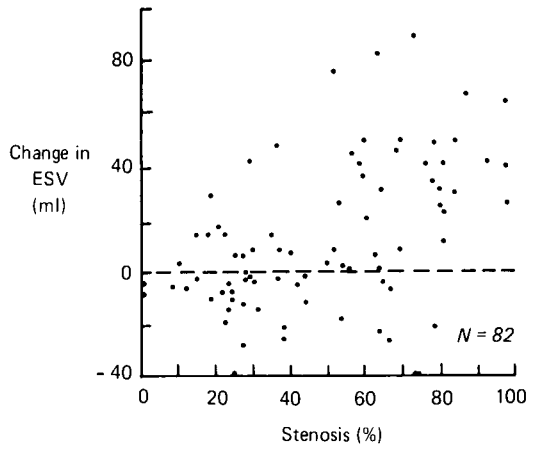


Figure 10. Change in left ventricular end-systolic volume (ESV) from rest to exercise compared with percent stenosis severity of 82 left anterior descending coronary artery lesions (41 patients).

Radionuclide studies with wall motion abnormalities during exercise were processed to separately determine anterior and posterior left ventricular ejection fraction. Of interest, mean anterior left ventricular ejection fraction did not significantly differ from mean posterior ejection fraction (0.61 ± 0.09 versus 0.62 ± 0.09) even though coronary lesions were isolated to the proximal left anterior descending artery. Of the 37 studies with abnormal wall motion, 5 demonstrated diffuse wall motion abnormalities. Twenty-five studies involved wall motion abnormalities at the apex, which may account for similarities in the anterior and posterior ejection fractions. Left ventricular end-systolic volume demonstrated a weaker correlation with percent diameter stenosis and minimal cross-sectional area than did exercise left ventricular ejection fraction (Fig. 10 and 11).

Discussion

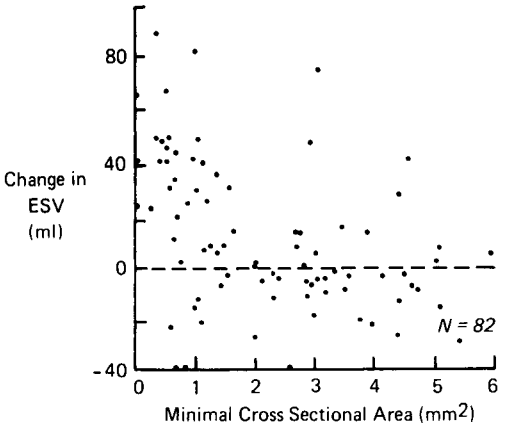
This investigation relates anatomic severity of coronary artery lesions and the resultant hemodynamic pressure gradients to cardiac function during stress. For lesions whose stenosis measurements were extreme, either minimal or markedly severe, the measurement of stenosis severity generally predicted the patient's functional response during exercise. Though group relations exist, the degree of individual variation in the relation of stenoses to exercise function is of interest. The greatest variation was in the patient group with stenosis of intermediate severity. Dynamic factors not accounted for by stenosis measurements may play an important role in determining why patients with similar stenosis severity and location may have a differing functional response to exercise.

The measurement of coronary stenosis severity has several limitations. Altered appearance in multiple views due to eccentricity, technical difficulties in image reproducibility and intraobserver variability are several factors that hamper the precise description of stenosis severity (13–16). Coronary arteries are not fixed rigid structures. Small dimensional differences in coronary lesions can result in large differences in flow (17,18). Particularly in eccentric ste-

Table 4. Exercise Left Ventricular Wall Motion Relative to Lesion Severity (82 measurements)

Percent Diameter Stenosis	Abnormal Wall Motion (%)	Normal Wall Motion (%)
<20 (n = 10)	10	90
20 to 50 (n = 30)	20	80
>50 (n = 42)	71	29

Figure 11. Change in left ventricular end-systolic volume (ESV) from rest to exercise compared with minimal cross-sectional area of 82 left anterior descending coronary artery lesions.



noses, where a portion of the vessel wall is functionally normal, changes in vascular tone or coronary artery spasm may significantly influence coronary artery blood flow (19,20). Differences between measurements of stenosis severity and their physiologic consequences cannot likely be explained solely by technical problems in obtaining these measurements.

Coronary stenosis versus coronary flow. In 1938 Mann et al. (21) introduced the concept that a certain critical stenosis is required before blood flow is reduced in a narrowed vessel. Clinical decisions regarding revascularization procedures often remain based on this concept. Yet, physiologic effects of a "fixed" coronary artery stenosis are dynamic. In their extensive study of the hyperemic response in dogs, Gould and colleagues (22,23) demonstrated that maximal coronary blood flow was markedly reduced by a constriction that did not affect rest flow. A stenosis of up to 85% may not affect rest flow whereas a stenosis of only 30% might alter maximal flow. In 1944 Shipley and Gregg (24) first demonstrated that the variations in peripheral resistance influenced the hydraulic resistance of a given stenosis. In the coronary circulation the dynamic impact of distal resistance may significantly influence the physiologic effects of a stenotic lesion. Several studies (18,25) have demonstrated that pharmacologically decreasing the resistance of the distal coronary circulation may actually increase the physiologic effects of a given coronary stenosis. The severity of a given stenosis must, therefore, be conceived of as dynamic in terms of its physiologic effects.

Coronary flow and pressure gradient. Gould et al. (26,27) showed that if flow increases across a fixed stenosis, the pressure gradient increases proportionally more than flow. Even small changes in systemic pressure, volume or velocity of coronary flow, or resistance of the distal myocardial vascular bed might yield marked changes in the gradient across a lesion. Banka et al. (28) reported an overall correlation between stenoses and gradient measurements. However, as in our investigation, a significant number of lesions with disparity between angiographic severity and gradient were observed. This could not be improved by accounting for the length of the stenotic lesion. Ganz et al. (29) reported a relatively poor correlation between pressure gradient at rest and angiographically defined degree of coronary stenosis. In their study, whereas angiographically severe stenoses were associated with large pressure gradients, a poor correlation existed for stenoses of moderate severity. Placement of currently available balloon dilation catheters across vascular stenoses has been shown to partially obstruct flow and lead to an overestimation of gradient severity (30). Bateman et al. (31) measured gradients directly in patients during the rewarming period after coronary artery bypass grafting. Analyses of their data reveal a poor correlation between stenosis severity and gradient (32). Again, consideration of the length of a stenotic lesion did not improve the correlation. The existence of physiologically significant collateral vessels may explain why the most severe gradient measurements were not associated with the most severe stenosis measurements in our study (Fig. 3). Hakki and Iskandrian and colleagues (33–36) thoroughly investigated the relations between severity of a coronary artery stenosis and consequent perfusion. In their studies patients with single vessel left anterior descending lesions of similar severity (>70% diameter stenosis) were found to have quantitative perfusion defects during exercise that were highly variable.

Coronary stenosis, ischemia and left ventricular function. The work of Tennant and Wiggers (37) in 1935 demonstrated in animals that gross functional abnormalities may appear within two beats of an ischemic insult. Measurements of global left ventricular function during exercise represent the sum expression of multiple and complex interactions of myocardial oxygen supply-demand relations. Multivariate analyses of first pass radionuclide data (12) have shown left ventricular ejection fraction during exercise to be the single best indicator of ischemic functional abnormalities due to coronary artery disease. The presence of coronary artery disease correlated better with exercise ejection fraction alone than with change in ejection fraction from rest to exercise. Factors such as coronary vessel dominance, degree of collateral circulation development, ventricular hypertrophy and endocardial to epicardial perfusion ratios may have led to significant differences in function between patients with lesions in the same location and with similar stenosis or gradient measurements.

Clinical implications. Static measurements of anatomy, such as stenosis, or isolated measurements of physiology, such as pressure gradient, do not fully reflect the dynamic metabolic balance of myocardial tissue at risk for ischemia. This raises the question as to which measurement is of greater clinical significance in the evaluation of coronary artery disease. Ultimately the most important criterion of clinical significance of a measurement is its impact on prognosis. Early reports of patients with coronary artery disease (38), at mean follow-up times of approximately 3 years, indicate that exercise left ventricular ejection fraction denotes a greater degree of prognostic information than does any anatomic measurement including the presence of left main or triple vessel disease. Future measurements of exercise cardiac function may be coupled with simultaneous analyses of coronary flow, perfusion and myocardial metabolism. Information derived from these studies will influence basic clinical decisions.

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